(MSF); this amendment is supported by disclosure throughout the specification, e.g., at page 1, line 18, to page 2, line 10; page 6, lines 5-11; page 26, lines 1-7; and page 30, line 27, to page 31, line 2, of the specification. The amendment to claim 19 is further supported by disclosure at page 4, lines 1-9, of the specification. Claims 10, 16, and 17 were amended for clarity as suggested by the examiner. The amendment to claim 13 is supported by disclosure at page 1, line 23, of the specification. The amendment to claims 40-41 is supported by disclosure at page 5, lines 24-25, of the specification. New claim 55 is supported by disclosure at page 14, lines 10-16, of the specification. New claims 56-59 are supported by disclosure at page 38, lines 8-13, of the specification, and Figs. 2A-B.

No new matter has been added.

35 U.S.C. § 102

Claims 1-3, 4, 5, 6, 19-29 and 40-41 were rejected for anticipation by Turner et al. (WO92/13075). The claims have been amended to distinguish the invention over the cited prior art. The claims now require a boundary-lubricating amount of MSF (SEQ ID NO:1) and/or a boundary-lubricating fragment of MSF.

Turner et al. describe MSF and certain alternatively spliced MSF and report that MSFs are capable of stimulating growth and development of colonies of megakaryocytes. Turner et al. fail to describe or suggest a boundary-lubricating activity of MSF or any fragment/splice variant with boundary-lubricating activity. Therefore, the amended claims are not anticipated by this reference.

35 U.S.C. § 112, first paragraph

Claims 1-6, 10-13, and 16-29 were rejected for overbreadth and lack of enablement. On page 2 of Paper No. 9, the Examiner states:

> Claims 1-6, 10-14, 16-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a tribonectin consisting of SEQ ID NO:1, having at least one O-linked lubricating moiety; does not reasonably provide enablement for any tribonectin that comprises a polypeptide that comprises an amino acid sequence of a spliced variant or a fragment sequence of SEQ ID NO:1.

Claims 20, 22, 24, and 26 have been canceled. Claim 1 has been amended to require a polypeptide containing the amino acid sequence of SEQ ID NO:1. Therefore, the rejection of claim 1 and claims, which depend from claim 1 should be withdrawn.

With respect to claims drawn to fragments or alternative splice variants of MSF, the Examiner states (page 3, lines 11-24, of Paper No. 9):

> The specification however, only discloses cursory conclusions (see pages 4-5, 10), without data to support the findings, which has listed the alternatively spliced variants of MSF (Table 3) and also states that a recombinantly or chemically-produced polypeptide containing at least exon 6 (but not exons 1 or 3) of MSF is useful to prevent and/or treat osteoarthritic disease. However, the specification fails to describe the specific structure (except amino acid sequences) and function of these variants. The specification indicates at page 4 that a tribonectin may contain a polypeptide, that comprises the amino acid sequences of residues 200-1140, or 200-1167, 200-1212, or 200-1263, inclusive, of SEQ ID NO:1 (claims 21, 23, 25, 27) or the amino acid sequence of which is 505 identical to 200-1140, or 200-1167, 200-1212, or 200-1263, inclusive, of SEQ ID NO:1, for examples (claims 20, 22, 24, 26). There are no indicia that the present application enables the full scope in view of the tribonectin that comprises the polypeptide sequence set forth in SEQ ID NO:1 and a fragment thereof as discussed in the following stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is encompassed.

Claims 20, 22, 24, and 26 (containing a reference to "50% identity") have been canceled.

The remaining rejected claims have been amended to define both structural limitations, i.e., by reciting specific amino acid sequences and post-translational modifications such O-linked oligosaccharides, and a functional limitation, i.e., boundary lubrication. For example, the amino acid coordinates required by claims 21, 23, 25, and 27 reflect data elucidating the differential

expression on MSF exons in lubricating MSF splice variants as well as data regarding structure/function relationships.

Contrary to the Examiner's assertion that the specification "discloses cursory conclusions... without data to support the findings", the specification discloses data that defines the structure of each naturally-occurring lubricating isoform. For example, the lubricating composition requires an MSF polypeptide with an O-linked oligosaccharide ("When the ultimate and penultimate sugars are removed from a naturally-occurring tribonectin purified from synovial fluid, the lubricating ability is eliminated"; page 23, lines 23-26, of the specification).

Exon 6 (encoding "mucin" repeat sequence KEPAPTT) is required for lubricating activity, because it provides the polypeptide scaffold to which the O-linked (Ser or Thr-linked) oligosaccharide is attached. For example, all of the naturally-occurring splice variants found in human synovial fluid contain an MSF sequence encoded by MSF exon 6 (page 38, lines 8-11, of the specification and Fig. 2A-B). In fact, all of the MSF isoforms identified in synovial fluid with normal lubricating activity contained the amino acid sequence encoded by at least exons 6-12 (amino acids 200-1404). In addition, each of the isoforms (MSF fragments) identified in human synovial fluid also contain the amino acid sequence encoded by MSF exon 1. Exon 1 encodes a domain that mediates binding of the tribonectin to hydrophobic surfaces like cartilage (page 38, lines 13-14, of the specification).

The claims are supported by this data pertaining to the identification of lubricating polypeptides of MSF and specific alternate splice variants encoded by the MSF gene. The amended claims require specific amino acid sequences and post-translational modifications demonstrated to be important in mediating lubricating activity. Therefore, the scope of the

amended claims is commensurate with the scope of disclosure and data provided in the specification. Withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, second paragraph

Claims 1-6, 10-13, 16-17, 19-27, and 40-41 were rejected for indefiniteness. Each objection is addressed below.

With respect to clams 1-2, the Examiner stated that the claims were "indefinite as to how a peptide structure is modified by an O-linked lubricating moiety". The claims were amended to recite "O-linked carbohydrate moiety." O-linked oligosaccharides, i.e., Ser/Thr-linked oligosaccharides, are directly linked to a serine or threonine residue via a O-glycosidic alpha-linkage. Such carbohydrate moieties and post-translational modification of a polypeptide (glycosylation) are well known in the art and described throughout the specification (e.g., at page 14, lines 18-29, of the specification).

Claim 10 was amended to delete "characterized by" as suggested by the examiner. The claim now requires that the tribonectin (MSF polypeptide containing O-linked carbohydrate moiety) reduce the coefficient of friction between two surfaces.

Claim 13 has been amended to delete the term "substantially" as suggested by the Examiner. The amended claim now specifies that the addition of a tribonectin to a solution does not increase the viscosity of the solution by more than 10%.

Claim 16 and 17 were amended to require that the glycosylation of the tribonectin is the presence of an O-linked oligosaccharide moiety.

Claim 19 was rejected for indefiniteness because of the term "fragment". The claim has been amended to recite a "boundary-lubricating fragment of MSF". The claim term "fragment is precisely defined in the specification: "A protein or polypeptide fragment is defined as a

polypeptide which has an amino acid sequence that is identical to part, but not all, of the amino acid sequence of a naturally-occurring protein or polypeptide from which it is derived, e.g., MSF" (page 4, lines 14-17, of the specification). The term is defined in the specification and is well known in the art. One of skill in the art would have no difficulty determining the meaning of the term "fragment of MSF". The claim has also been amended to require that the fragment is a boundary-lubricating fragment, i.e., it possess lubricating activity.

Claims 20-27 were rejected for indefiniteness because of the use of the term "inclusive". Claims 20, 22, 24, and 26 have been canceled. The claim term "inclusive" has been deleted. Claims 21, 23, 25, and 27 (which require specific amino acid sequences of MSF fragments) were amended to depend from claim 19, which is drawn to a boundary-lubricating MSF fragment.

In view of the foregoing amendments, Applicants submit that the rejection under 35 U.S.C § 112, second paragraph, should be withdrawn.

CONCLUSION

This application is believed to be in condition for allowance, and a statement to this effect is respectfully requested.

A petition for extension of time and a check in the amount of $460.00 is enclosed to cover the petition fee for a three month extension of time pursuant to 37 C.F.R. § 1.17(a)(3). The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21486-026CIP.

Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at (617) 542-6000.

Respectfully submitted,

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EXHIBIT A

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1. A tribonectin comprising a boundary-lubricating amount of a polypeptide, said polypeptide comprising the amino acid sequence of SEQ ID NO:1 and at least one O-linked oligosaccharide [lubricating] moiety.

2. The tribonectin of claim 1, wherein said moiety is a β(1-3)Gal-GalNAc moiety.

3. [The tribonectin of claim 1, wherein said tribonectin] A tribonectin comprising a boundary-lubricating amount of a fragment of SEQ ID NO:1, wherein said fragment comprises amino acids 1 to 24 and 200 to 1404 of SEQ ID NO:1[, wherein said tribonectin] and lacks amino acids 25-199 of SEQ ID NO:1.

4. [The tribonectin of claim 1, wherein said tribonectin] A tribonectin comprising a boundary-lubricating amount of a fragment of SEQ ID NO:1, wherein said fragment comprises amino acids 1 to 156 and 200 to 1404 of SEQ ID NO:1[, wherein said tribonectin] and lacks amino acids 157-199 of SEQ ID NO:1.

5. [The tribonectin of claim 1, wherein said tribonectin] A tribonectin comprising a boundary-lubricating amount of a fragment of SEQ ID NO:1, wherein said fragment comprises amino acids 1 to 106 of SEQ ID NO:1 and 200-1404 of SEQ ID NO:1[, wherein said tribonectin] and lacks amino acids 107 to 199 of SEQ ID NO:1.

6. [The tribonectin of claim 1, wherein said tribonectin] A tribonectin comprising a boundary-lubricating amount of a fragment of SEQ ID NO:1, wherein said fragment comprises amino acids 1 to 25 of SEQ ID NO:1, 67 to 106 of SEQ ID NO:1 and 200-to 1404 of SEQ ID NO:1 [wherein said tribonectin] and lacks amino acids 26 to 66 of SEQ ID NO:1.

10. The tribonectin of claim 1, wherein said tribonectin [is characterized as reducing] reduces the coefficient of friction between bearing surfaces.

11. The tribonectin of claim 1, wherein said tribonectin is characterized as reducing the coefficient of friction between bearing surfaces in vitro.

12. The tribonectin of claim 1, wherein said tribonectin is characterized as reducing the coefficient of friction between bearing surfaces in vivo.

13. The tribonectin of claim 1, wherein addition of said tribonectin to a solution does not [substantially] increase the viscosity of [a solution to which it is added] said solution by more than 10%.

16. The tribonectin of claim 1, wherein at least 10% of said tribonectin is glycosylated by said O-linked oligosaccharide moiety.

17. The tribonectin of claim 1, wherein at least 40% of said tribonectin is glycosylated by said O-linked oligosaccharide moiety.

18. The tribonectin of claim 19, wherein the molecular weight of said tribonectin is in the range of 200-280 kDa.

19. [The tribonectin of claim 1, wherein said polypeptide comprises a] A composition comprising a boundary-lubricating amount of a fragment of megakaryocyte stimulating factor.

21. The [tribonectin] fragment of claim 19, wherein said [polypeptide] fragment comprises the amino acid sequence of residues 200-1140[, inclusive,] of SEQ ID NO:1.

23. The [tribonectin] fragment of claim 19, wherein said [polypeptide] fragment comprises the amino acid sequence of residues 200-1167[, inclusive,] of SEQ ID NO:1.

25. The [tribonectin] fragment of claim 19, wherein said [polypeptide] fragment comprises the amino acid sequence of residues 200-1212[, inclusive,] of SEQ ID NO:1.

27. The [tribonectin] fragment of claim 19, wherein said [polypeptide] fragment comprises the amino acid sequence of residues 200-1263[, inclusive,] of SEQ ID NO:1.

28. The [tribonectin] fragment of claim 19, wherein said [polypeptide] fragment lacks the amino acid sequence of residues 1-24[, inclusive,] of SEQ ID NO:1.

29. The [tribonectin] fragment of claim 19, wherein said [polypeptide] fragment lacks the amino acid sequence of residues 67-104[, inclusive] of SEQ ID NO:1.

40. A biocompatible composition comprising a tribonectin, wherein said composition is [in a form suitable for the inhibition of tissue adhesion formation] a film, membrane, foam, gel, or fiber.

41. The composition of claim 40, wherein said tribonectin is [in the form of] a membrane, foam, gel, or fiber.

55. The tribonectin of claim 1, further comprising hyaluronic acid.

56. A composition comprising a boundary-lubricating polypeptide encoded by a nucleic acid consisting essentially of exon 1, 2, 3, 4, and 6-12 of a human MSF gene.

57. A composition comprising a boundary-lubricating polypeptide encoded by a nucleic acid consisting essentially of exon 1, 2, 3, and 6-12 of a human MSF gene.

58. A composition comprising a boundary-lubricating polypeptide encoded by a nucleic acid consisting essentially of exon 1, 3, and 6-12 of a human MSF gene.

59. A composition comprising a boundary-lubricating polypeptide encoded by a nucleic acid consisting essentially of exon 1 and 6-12 of a human MSF gene.